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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,294	01/22/2004	Thomas R. Porter	UNMC/0014	8260

7590 06/16/2005

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EXAMINER	
JAWORSKI, FRANCIS J	

ART UNIT	PAPER NUMBER
3737	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,294	PORTER ET AL	
	Examiner	Art Unit	
	Jaworski Francis J.	3737	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 .S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

[Parenthesized claim numbers following a rejection statement identify the specific claim or claims towards which the statement is directed.]

Claims 1 – 4, 6 – 15, 22 – 24 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Villanueva et al (WO 99/13918, of record as citation B10 of the IDS filed on 1-22-2004) in view of Averkiou et al (US6171246).

1) In a first or semantic basis for rejection the Examiner has noted that in a broadest reasonable interpretation one might loosely refer to plaque or to the diseased vascular endothelium of an artery burdened with plaque during overt obstructive protrusion into the vessel as 'dysfunctional' meaning 'disease-involved' endothelium

whereupon a microbubble or contrast agent-based scan made during an acute MI or as an angioplasty adjunct would therefore be 'dysfunctional epithelium imaging'. Thus Villanueva et al page 1 bottom suggests a method of imaging dysfunctional vascular endothelium during the obstructive or occluded stage where reduced clearance of the bubbles reflects the very flow impediment that the study is examining, and then later on page 21 TABLE 1 and lines 14 – 16 suggests that a relatively low energy of pulse repetition scanning is useful to perform imaging without rupture of the bubbles.

Whereas in the aforementioned passage and table in Villanueva et al is silent as to low 'mechanical index' which by definition pertains to peak rarefaction pressure of the ensonating wave divided by the sqr-root of the transmission frequency and not to an energy criteria based upon total power output or intensity at the emitting face of the transducer, it would have been obvious in view of Averkiou et al col. 6 lines 1 – 26 to image with a contrast agent at .1 MI or less since this was known to be a mechanical peak pressure index insufficient to provoke rupture of microbubbles as Villanueva et al is calling for such insufficiency, and in the identical general context of assessing perfusion rates of bloodflow associated with myocardium, see Averkiou et al col. 1 lines 25 – 28.

2) In a second or core basis for rejection the Examiner has applied a narrower definition of 'dysfunctional vascular endothelium' intimated in Villanueva et al page 5 lines 7 – 15 and applicants' specification para [0002] namely as defining that state of early impaired vasodilation/altered chemotactic properties or prothrombin/leukocyte adhesiveness/inflammatory cytokine expression prior to gross morphologic changes in

the vascular endothelium, i.e. dysfunction largely prior to infiltration and plaque growth. Then, since Villanueva et al is not merely exploring causes for this dysfunctioning by in vitro studies with tailored binding molecules but attempting to explain the prior observation that during microbubble contrast agent imaging that microbubble retention within the vessel does occur (page 6 lines 8 – 15) and with the expressed purpose of extending contrast agent angiography to such functional studies (page 5 lines 12 – 15) and at a reduced energy level ensonation which under the prior argument above may reasonably be modified by Averkiou et al to pertain to a type of low MI scanning perfusion study, the in vivo or in situ limitation of "in a vessel of interest in an individual" is met.

A re-statement of this argument is that Villanueva et al's claim 5 might reasonably be extended to microbubble imaging of intact, in situ coronary vascular tissue, and under low MI modification as taught by Averkiou et al. (Claims 1 – 4).

Villanueva et al in and of itself teaches use of at least

- lipids (page 14 lines 18 – 21) and surfactants (page 27 line 19) (Claim 6)
- proteins including albumin (page 28 line 17) (Claims 7-8)
- biodegradable polymers such as polyethylene glycol polymers and oligomers (page 14 lines 22 – 29)(Claim 9)
- polysaccharide (page 17 line 11) (Claim 10)
- phosphatidic acid (page 15 line 10) (Claims 11 - 12)
- gas-filled microbubbles per Example 1a using perfluorobutane as the halogenated hydrocarbon (Claims 13 - 15).

- Villanueva et al contemplated use of greater than 3 micron microbubbles at a 3.5 Mhz ensonation frequency , see page 20 line 27.Applicants are understood to be referring to Mhz to constitute imaging ultrasound frequencies. (Claims 22 -24).

Claim 5 is again rejected under 35 U.S.C. 103(a) as being unpatentable over Villanueva et al in view of Porter et al as applied to claim 4 above, and further in view of Widlansky et al (JACC 10/2003, citation 3 of the 09-02-2004 IDS) since whereas the former are silent as to literal recitation of activity on the carotid artery, Villanueva et al is directed to early atherosclerotic process diagnosis throughout the vasculature, see page 2 bottom para, and Widlansky merely evidences in the broad sense that cerebrovascular disease is embraced by such dysfunctional vascular endothelial study which disease in context would refer to the contributing infeed carotid artery sets. (Claim 5).

Claims 16 – 21, 26 – 36 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Villanueva et al in view of Averkiou et al as applied to claim 1 above, and further in view of Porter et al (US5567415) . Whereas the former are silent as to sugar solution constituents, it would have been obvious in view of Porter et al col. 3 lines 13 – 32 to use sugar solution including dextrose with albumin in standard mixture ratios and perfluoropropane gas under sonication in order to perform vascular imaging. (Claims 16 – 21)..

Otherwise the rationale for the base reference combination yet applies as does the aforenoted microbubble size range and ensonation frequency in Villanueva et al. (Claims 26 – 36).

Claim 25 is again rejected under 35 U.S.C. 103(a) as being unpatentable over Villanueva et al in view of Averkiou et al as applied to claim1 above, and further in view of Holley et al (US6626831). It would have been obvious in view of the latter that a 20 – 30 Hz frame rate is desirable in imaging systems such as Villanueva et al and Averkiou et al which do not mention such a range since this allows visual persistence to track continuous motion in moving organs such as the heart or main vasculature. (Claim 25).

Claim 37 is again rejected under 35 U.S.C. 103(a) as being unpatentable over Villanueva et al in view of Averkiou et al and Porter et al as applied to claim 26 above, and further in view of Holley et al, for reasons as set forth immediately above. (Claim 37)..

Response to Arguments

Applicants' arguments have not been found persuasive because with respect to the semantic argument that contrast agent imaging in and of itself is a form of qualitative identification of dysfunctional vessel endothelium and in later stages of atherosclerosis because Villanueva page 6 lines 8-15 notes that conventional imaging produces qualitative identification of sites of endothelial dysfunction by virtue of microbubble lingering, and of course later stage obstructive changes would be readily visualized. Assuming however that some degree of language specificity were present in the claims

which negatived this broad interpretation and that a tagged microbubble or other specialized approach were required to quantitatively identify a pathologic dysfunctional vessel then Villanueva et al teaches that the application of ensonating ultrasound should be made first at very low intensity levels and then gradually increasing same in order to avoid rupture-attriting the microbubble population, see page 20 lines 18-22. Averkiou et al merely evidences that the claimed low mechanical index range would be an obvious one for visualizing microbubbles without rupture.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication should be directed to Jaworski Francis J. at telephone number 571-272-4738

FJJ:fjj

12-11-2004

Francis J. Jaworski
Primary Examiner